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# Safety of budesonide/formoterol maintenance and reliever therapy in asthma trials

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**Summary**
*Background:* The safety of long-acting $\beta_2$-agonists (LABAs) in asthma is debated. This study examined the safety of the inhaled corticosteroid (ICS)/LABA combination budesonide/formoterol dry powder inhaler used as maintenance and reliever therapy versus combination treatments based on guideline recommendations.
*Methods:* Safety data from six double-blind, randomised clinical trials (RCTs) in asthma where budesonide/formoterol was used as maintenance and reliever therapy for at least 6 months were reviewed ($N = 14\,346$). All-cause mortality and asthma-related serious adverse events (SAEs) (co-primary endpoints), overall and cardiac SAEs, and discontinuations due to adverse events (DAEs) were assessed. Estimated Mantel–Haenszel (MH) relative risks (RR) with this regimen versus comparators were calculated.
*Results:* There was no increase in all-cause mortality with budesonide/formoterol maintenance and reliever therapy (four deaths [0.07%] versus nine [0.10%]; pooled MH RR 0.70, 95% confidence interval [CI] 0.21–2.30). Asthma-related SAEs were reduced with budesonide/formoterol maintenance and reliever therapy: 41 (0.73%) versus 121 (1.38%); pooled MH RR 0.59, 95% CI 0.42–0.85. All-cause and asthma-related DAEs were also reduced with budesonide/formoterol maintenance and reliever therapy: pooled MH RR 0.60 (95% CI 0.46–0.79) and 0.43 (0.28–0.68), respectively. Overall and cardiac-related SAEs were comparable between treatment groups: pooled MH RR 0.96 (95% CI 0.82–1.14) and 1.26 (0.72–2.22), respectively.
*Conclusion:* Budesonide/formoterol dry powder inhaler maintenance and reliever therapy was well tolerated in RCTs versus fixed-dose alternatives and not associated with increased risk of death or cardiac-related SAEs and DAEs, and asthma-related SAEs and DAEs were significantly reduced. Given the limitations of RCTs, particularly exclusion of patients with co-morbidities, ongoing surveillance is appropriate.


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## Introduction

Guidelines for management of asthma focus on the goals of overall asthma control, i.e. achieving current control and reducing future risks. Optimal current control is characterised by infrequent symptoms, only occasional rescue bronchodilator use, lung function at or near normal stable levels, and normal physical activity levels. Reduced future risk is characterised by preventing exacerbations, lung function decline and medication adverse effects.[1–3] The recent Global Initiative for Asthma (GINA) guidelines use the characteristics of current control noted above to classify patients as having Controlled, Partly Controlled or Uncontrolled asthma. Addition of a long-acting $\beta_2$-agonist (LABA) is recommended if patients are inadequately controlled on low to moderate doses of inhaled corticosteroid (ICS) alone.[3] Trials of combination therapy with a LABA and an ICS in separate inhalers or, more recently, in fixed-dose formulations of budesonide/formoterol (Symbicort®) or salmeterol/fluticasone (Seretide™ and Advair™) have consistently reported increased proportions of patients with good asthma control and reduced future risk of exacerbations compared with increasing the dose of ICS alone.[4–6]

A more recent development for employing combination ICS/LABA treatment (outside of the U.S.) is the use of budesonide/formoterol dry powder inhaler (DPI) (Turbuhaler®[c]) as both maintenance and reliever therapy (Symbicort SMART®[d]). This strategy, which is now included in the GINA treatment guidelines for asthma, uses a fixed-dose combination of budesonide and formoterol for maintenance therapy supplemented with additional doses of the same combination rather than a separate short-acting $\beta_2$-agonist (SABA) when reliever therapy is needed. The therapeutic concept is that this strategy provides additional anti-inflammatory therapy when symptoms begin to develop, thus further reducing exacerbations, eliminates the need for a separate SABA inhaler[7] and may allow lower doses of ICS and LABA during periods when asthma is stable.

Six large, double-blind, randomised clinical trials involving more than 14 000 asthma patients have shown that budesonide/formoterol maintenance and reliever therapy reduces severe asthma exacerbations compared with higher maintenance doses of ICS[6,8,9] or combinations of higher-dose ICS with LABA[10,11] or same-dose ICS with LABA,[6,12] all used with SABA as needed for relief. In addition to the gains in efficacy, health economic analyses have shown beneficial results for budesonide/formoterol maintenance and reliever therapy.[13–15] Recently, several open-label studies of budesonide/formoterol maintenance and reliever therapy that more closely mirror 'real-world' settings[16,17] have reported that this strategy improved asthma control and was associated with fewer exacerbations compared with other guideline-based regimens of conventional best practice selected by the patient's physician.

During recent years, the relationship between the use of LABAs and asthma mortality and morbidity has been heavily debated.[18–20] The use of LABAs without concomitant ICS is of concern, as studies report increased asthma-related mortality and serious adverse events (SAEs)[20] with LABA monotherapy, most probably as a consequence of the masking of, and risk resulting from the undertreatment of, underlying inflammation.[21] International guidelines, and a recent FDA review panel, recommend that LABAs should only be used in combination with an appropriate dose of ICS.[3] The strategy of using budesonide/formoterol as both maintenance and reliever therapy obviates the potential risk of LABA monotherapy in that ICS is delivered with each dose of formoterol, and so should improve the benefit/risk ratio of LABA therapy.

We have reviewed the safety data reported in clinical trials in adolescents and adults with asthma in six double-blind trials[6,8–12] in which budesonide/formoterol DPI was used as maintenance and reliever therapy. The incidence of mortality and morbidity was compared with that observed for a range of comparator treatments including budesonide, budesonide/formoterol or salmeterol/fluticasone used as maintenance therapy combined with a SABA, or in one trial formoterol,[12] as reliever therapy. As a supplementary analysis, data from seven open-label trials were analysed separately. The purpose of this paper is to examine the safety of a new treatment regimen versus standard guideline-based treatments for asthma.

## Methods

### Data source

All double-blind AstraZeneca trials in patients with asthma involving the use of budesonide/formoterol as maintenance and reliever therapy for at least 6 months were identified through the company database. Of 14 346 patients randomised into the six trials, 5584 used budesonide/formoterol as maintenance and reliever therapy and 8762 used comparator treatments, namely guideline-based treatment regimens for moderate to severe, persistent asthma, including use of regular budesonide, budesonide/formoterol or salmeterol/fluticasone, all with a SABA or formoterol as reliever medication.[6,8–12] Five of the trials enrolled patients aged 12–89 years (although four patients aged 11 years were enrolled erroneously) and one trial[6] also enrolled children aged 4–11 years. The mean age was 39.4 years (range 4–89 years), 5921 patients (41%) were male and the distribution by ethnic origin was 74% Caucasian, 17% Oriental, 1% Black and 8% of other race.

Data from seven open-label trials with 9890 patients were analysed separately.

### Outcome events

All-cause mortality and asthma-related SAEs were co-primary endpoints. Secondary outcomes were overall SAEs, cardiac-related SAEs, discontinuations due to adverse events (DAEs), and asthma-related and cardiac-related

[c] Turbuhaler® is a trademark owned by AstraZeneca. The dry powder formulation Turbuhaler is currently not approved in the U.S.
[d] Symbicort SMART® is a trademark owned by AstraZeneca. The Symbicort SMART posology is currently not approved in the U.S.

DAEs. All these events were evaluated at the time by the investigators involved in each study and prior to unblinding. All fatalities in all trials were reassessed by the present authors and categorised as asthma-related, cardiac-related or due to other reasons. Adverse events commonly observed with $\beta_2$-agonists and ICS were recorded in all studies and have been summarised and presented as additional safety information.

Asthma-related events were defined as any event coded to the preferred terms *asthma*, *status asthmaticus* or *bronchospasm* according to the Medical Dictionary for Regulatory Activities (MedDRA) version 8.0. In addition, one death in the trial by Kuna et al.,[11] coded by the trial investigator as due to respiratory failure, was considered by the current authors as asthma-related. Cardiac-related events were defined as any event coded using MedDRA v 8.0 according to the terms in Table E1, on-line supplement.

SAEs (asthma- and cardiac-related) were defined using the International Conference on Harmonisation recommendations, i.e. any adverse event that was immediately life threatening, required inpatient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability or incapacity, was a congenital abnormality/birth defect or was an important medical event that may jeopardise the subject or require medical intervention to prevent one of the outcomes listed above.

Events were counted as the number of patients reporting at least one such event. When multiple events were recorded, a patient was counted once for each group of adverse events. Thus, a patient reporting both angina pectoris and hypertension would be counted once in the group of cardiac-related events, while a patient reporting two asthma attacks and one angina pectoris would be counted once among the asthma-related events and once among the cardiac-related events.

Deaths and DAEs were represented by the event resulting in the death or discontinuation. Deaths during treatment were included among the SAEs, DAEs and adverse events. For SAEs and adverse events, multiple occurrences of the same event were counted as the first incidence of the event.

### Data analyses

For each patient, the person-time of participation in the trial was measured and cumulated to obtain person-years of exposure. The rates of events were expressed per 1000 treatment years (TTY) computed for each treatment group, ignoring the very small number of patients with multiple events of the same type. Due to the very small number of deaths, statistical methodology was only applied to all-cause mortality, while categorised deaths are presented descriptively. Overall relative risk (RR) was analysed using a stratified Mantel–Haenszel (MH) approach adjusted for treatment exposure, which allowed for possible differences between trials, thereby reducing bias. This provided the pooled MH RR and 95% confidence interval (CI) for each outcome event. For individual studies, a descriptive 95% credibility interval for the RR was provided using the method of Barker and Cadwell with an uninformative uniform prior; the median of the posterior distribution was used to provide a point estimate for the RR.[22] These Bayesian risk estimates and credibility intervals are presented in Forest-plots, together with the pooled MH RR and its 95% CI for each outcome event. In Table E2 in the on-line supplement, the MH RR and 95% CI, when calculable, are presented for each outcome event for each trial. In addition, the reporting of asthma-related SAEs over time was analysed using a Cox regression model, stratified by study, and displayed using a Kaplan–Meier survival curve.

Because adverse events may be greater among older subjects, a sub-group analysis was performed restricted to those aged 50 years and older.

For RRs, differences were considered statistically significant when the 95% CI excluded 1.00.

Formoterol doses are expressed as delivered doses. Formoterol delivered doses of 9 μg and 18 μg correspond to metered doses of 12 μg and 24 μg, respectively.

## Results

### Number of trials and patients

Details of the clinical trials included in the safety database, comparator treatments in each of the trials, corresponding treatment years, daily delivered doses of maintenance ICS/LABA therapy, and percentage of days with at least four as-needed inhalations are shown in Table 1.[6,8–12] Because there were multiple arms in some of the clinical trials, the number of patients in the comparator groups ($n = 8762$) exceed those in the budesonide/formoterol maintenance and reliever therapy groups ($n = 5584$). The distribution of patients by number of trials and comparator treatments and the exposure time is shown in Fig. 1. Total exposure time for the budesonide/formoterol maintenance and reliever therapy group was 3.94 TTY versus 6.29 TTY for the combined comparator group.

### Deaths

Death was reported for four patients (0.07%) in the budesonide/formoterol maintenance and reliever therapy arm of the study and for nine controls (0.10%); none were attributed by the investigator to the study medication. Two were deemed to be asthma-related (one in each group) and four deaths cardiac-related (all in the comparator group). There was no increase in the risk for any specific type of death with budesonide/formoterol maintenance and reliever therapy compared with alternative treatments (Table 2). The pooled exposure-adjusted MH RR for all-cause death was 0.70 (95% CI 0.21–2.30) as shown in Table 2 and Fig. 2. (Numeric data for RRs and 95% CIs for all outcome variables per trial are presented in Table E2 in the on-line supplement.)

### Asthma-related serious adverse events

Asthma-related SAEs were significantly reduced with budesonide/formoterol maintenance and reliever therapy compared with comparator therapy: 41 (0.73%) versus 121 (1.38%); pooled MH RR 0.59, 95% CI 0.42–0.85 (Table 3 and Fig. 2).

Kaplan–Meier survival curves indicated a clear separation between treatment groups and a prolonged time to the event

**Table 1** Clinical trial design and patient numbers contributing to analyses.

| Study | Duration (months) | BUD/FORM maintenance and reliever therapy | Comparators | BUD/FORM maintenance and reliever therapy | | | Comparators with daily delivered dose plus as-needed medication | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Number of patients (exposure in TTY) | | Daily delivered dose by protocol (+ BUD/FORM prn) | Average daily dose of FORM | Days with at least four as-needed inhalations (%)[a] | BUD (+ TERB prn) | BUD/FORM | SAL/FLU (+ SALB prn) |
| Scicchitano 2004[9] | 12 | 947 (0.85) | 943 (0.83) | 320/9 | ~ 13 | 3 | 640 | | |
| O'Byrne 2005[6] | 12 | 922 (0.84) | 1831 (1.64) | 160/9 (80/4.5)[b] | ~ 13 | 3 | 640 | 160/9[b] + TERB prn | |
| Rabe 2006A[8] | 6 | 354 (0.17) | 342 (0.16) | 160/9 | ~ 13 | 4 | 320 | | |
| Rabe 2006B[12] | 12 | 1107 (1.03) | 2275 (2.10) | 320/9 | ~ 13 | 6 | | 320/9 + TERB prn<br>320/9 + FORM prn | |
| Kuna 2007[11] | 6 | 1103 (0.50) | 2218 (1.00) | 320/9 | ~ 13 | 7 | | 640/18 + TERB prn | 100/500 |
| Bousquet 2007[10] | 6 | 1151 (0.55) | 1153 (0.54) | 640/18 | ~ 23 | 7 | | | 100/1000 |
| TOTAL | | 5584 (3.94) | 8762 (6.29) | | | | | | |

BUD/FORM = budesonide/formoterol; SAL/FLU = salmeterol/fluticasone; TERB = terbutaline; FORM = formoterol; SALB = salbutamol; prn = as needed; TTY = 1000 treatment years. All doses are expressed as total daily doses in μg. All trials were double blind.

[a] Four as-needed inhalations results in a dose per day of 27 μg of formoterol for the first five trials and of 36 μg in the trial by Bousquet et al.

[b] Patients aged 4–11 years used half the maintenance medication.

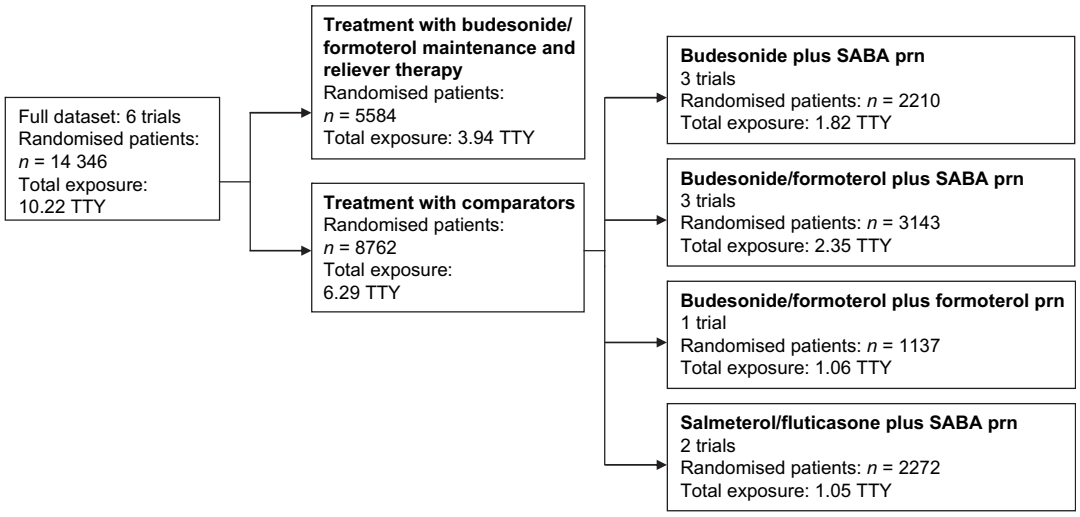


**Figure 1** Flow-chart of randomised patients. prn = as needed; SABA = short-acting $\beta_2$-agonist; TTY = 1000 treatment years.

in the budesonide/formoterol maintenance and reliever therapy group compared with the comparator group (Fig. 3). According to a log-rank test, stratified by study, the risk at any particular time point was lower in the budesonide/formoterol maintenance and reliever therapy group compared with the comparator group ($p = 0.004$). In a Cox regression model, also stratified by study, the hazard ratio was estimated as 0.59 (95% CI 0.42—0.85, $p = 0.004$), corresponding to a 41% lower risk with budesonide/formoterol maintenance and reliever therapy compared with comparator treatment at a particular time point during the follow-up.

## Cardiac-related and other serious adverse events

The reporting of cardiac-related SAEs was low in both treatment groups with a numerically higher rate with budesonide/formoterol maintenance and reliever therapy: 23 (0.41%) versus 27 (0.31%), yielding a pooled MH RR of 1.26 and a 95% CI of 0.72—2.22. Overall reporting of SAEs due to any cause was similar between the treatment groups, 4.2% and 4.5% respectively, with a pooled MH RR close to 1 (Table 3 and Fig. 4).

## Discontinuations due to adverse events

All-cause DAEs and asthma-related DAEs were reduced with budesonide/formoterol maintenance and reliever therapy compared with alternative treatments: pooled MH RR 0.60 (95% CI 0.46—0.79) and 0.43 (0.28—0.68), respectively. Cardiac-related DAEs were numerically but not statistically significantly lower among patients in the budesonide/formoterol maintenance and reliever therapy group: 8 (0.14%) versus 15 (0.17%); MH RR 0.73 (95% CI 0.30—1.73) (Table 3 and Fig. 4).

## Adverse events commonly observed with $\beta_2$-agonists or inhaled corticosteroid therapy

There were no notable differences observed between the two treatment groups with regard to adverse events commonly observed with $\beta_2$-agonists or ICS therapy (Table 4).

## Results versus the individual comparators

As a sensitivity analysis, the incidence of all endpoints was stratified by type of comparator. Thus, the budesonide/formoterol maintenance and reliever therapy treatment arms from the three trials with a budesonide plus SABA as-needed treatment arm[6,8,9] were combined to give 2223 patients on budesonide/formoterol maintenance and reliever therapy versus 2210 on budesonide plus SABA as needed. Similar groupings were made for comparisons with budesonide/formoterol plus SABA as needed[8,11,12] (3132 patients versus 3143 patients), budesonide/formoterol plus formoterol as needed[12] (1107 versus 1137 patients) and salmeterol/fluticasone plus SABA as needed[10,11] (2254 versus 2272 patients). For all-cause mortality, the number

**Table 2** Rates and ratios of cause-specific death across six randomised controlled trials.

| | BUD/FORM maintenance and reliever therapy: $N = 5584$; exposure = 3.94 TTY | | Comparators: $N = 8762$; exposure = 6.29 TTY | | RR (95% CI)[a] |
|---|---|---|---|---|---|
| | Deaths (%) | Rate per TTY | Deaths (%) | Rate per TTY | |
| Asthma-related death | 1 (0.02) | 0.25 | 1 (0.01) | 0.16 | |
| Cardiac-related death | 0 | 0 | 4 (0.05) | 0.64 | |
| Other deaths | 3 (0.05) | 0.76 | 4 (0.05) | 0.64 | |
| Total deaths | 4 (0.07) | 1.02 | 9 (0.10) | 1.43 | 0.70 (0.21—2.30) |

BUD/FORM = budesonide/formoterol; CI = confidence interval; RR = risk ratio TTY = 1000 treatment years.
[a] Mantel—Haenszel relative risk for budesonide/formoterol maintenance and reliever therapy versus comparators.

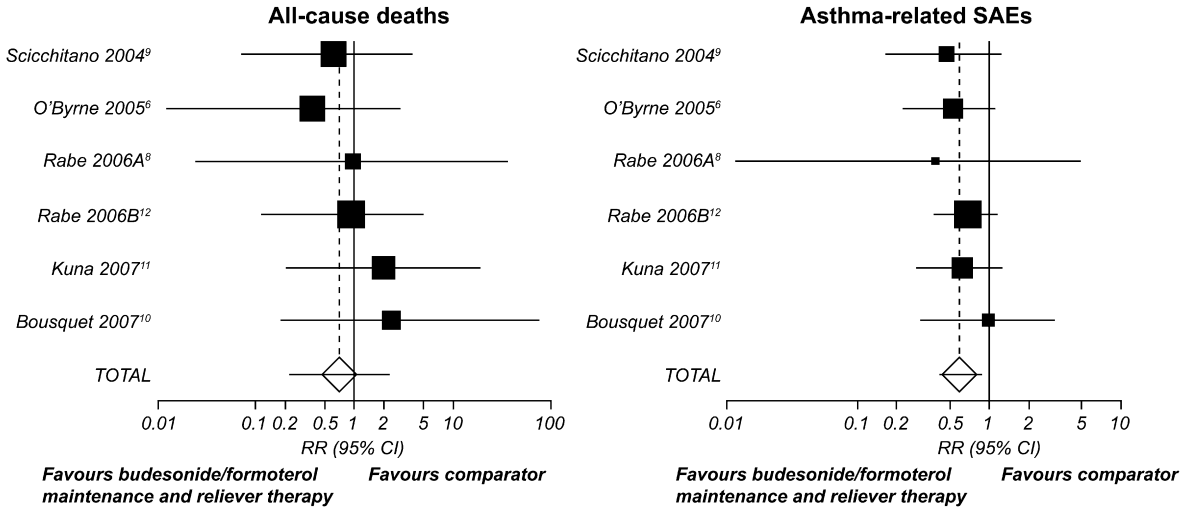


**Figure 2** Forest-plots of Mantel–Haenszel relative risks for primary outcome events. CI = confidence interval; RR = risk ratio; SAE = serious adverse event.

of events became too low for any meaningful comparisons to be made. For the co-primary endpoint, asthma-related SAEs, all four comparisons gave results favouring budesonide/formoterol maintenance and reliever therapy, with reductions ranging from 28% (versus budesonide/formoterol plus formoterol as needed) to 50% (versus budesonide plus SABA as needed). The results are presented in Tables E3–E6 in the on-line supplement.

### Results in patients aged 50 years and older

Among the 4347 subjects aged 50 years and older, findings were similar to those for the whole study population (Table E7 in the on-line supplement).

### Results from open-label trials

As a supplementary analysis, we analysed data from seven open-label trials.[16,23] In these trials, 4963 patients treated with budesonide/formoterol maintenance and reliever therapy (total exposure 2.9 TTY) were compared with patients treated with salmeterol/fluticasone plus SABA as needed ($n$ = 1071; 1.0 TTY) or conventional best practice, as judged by the investigator ($n$ = 3856; 1.9 TTY). There were four deaths with budesonide/formoterol maintenance and reliever therapy versus five deaths with comparator treatments, none of which were asthma-related. Asthma-related SAEs were numerically lower among patients treated with budesonide/formoterol maintenance and reliever therapy ($n$ = 24; 0.49%) than among those treated with the comparators ($n$ = 32; 0.65%) (Table E8 in the on-line supplement).

## Discussion and conclusions

In this trial database of 14 346 patients participating in randomised, double-blind, controlled trials, the number of all-cause deaths and asthma-related SAEs (the two co-primary endpoints) were lower among patients who received budesonide/formoterol maintenance and reliever therapy compared with those who received alternative treatments. The risks for asthma-related SAEs and DAEs and overall DAEs were significantly reduced by budesonide/formoterol maintenance and reliever therapy (by 41%, 57%

**Table 3** Asthma-related and cardiac-related serious adverse events and discontinuations due to adverse events across six randomised controlled trials

| | BUD/FORM maintenance and reliever therapy: $N$ = 5584; exposure = 3.94 TTY | Comparators: $N$ = 8762; exposure = 6.29 TTY | RR (95% CI)[b] |
|---|---|---|---|
| | N[a] (%) | N[a] (%) | |
| Asthma-related SAEs | 41 (0.73) | 121 (1.38) | 0.59 (0.42–0.85) |
| Cardiac-related SAEs | 23 (0.41) | 27 (0.31) | 1.26 (0.72–2.22) |
| Patients with any SAE | 233 (4.17) | 392 (4.47) | 0.96 (0.82–1.14) |
| Asthma-related DAEs | 25 (0.45) | 85 (0.97) | 0.43 (0.28–0.68) |
| Cardiac-related DAEs | 8 (0.14) | 15 (0.17) | 0.73 (0.30–1.73) |
| Patients with any DAE | 75 (1.34) | 183 (2.09) | 0.60 (0.46–0.79) |

BUD/FORM = budesonide/formoterol; CI = confidence interval; DAE = discontinuation due to adverse event; RR = risk ratio; SAE = serious adverse event; TTY = 1000 treatment years.

[a] Number of patients reporting at least one SAE or number of patients reporting DAE.

[b] Mantel–Haenszel relative risk for budesonide/formoterol maintenance and reliever therapy versus comparators.

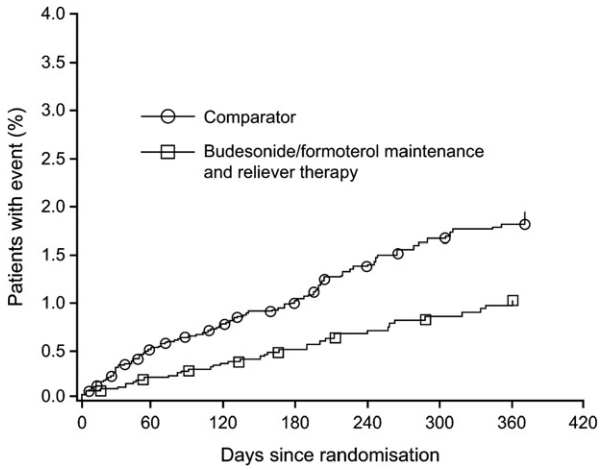


**Figure 3** Kaplan–Meier survival curves showing time to first asthma-related serious adverse event.

and 40%, respectively) and the time to the first asthma-related SAE was increased by 41%. The risks for cardiac-related DAEs and SAEs and overall SAEs were similar between the two treatment groups. It is important to note that all but one of the comparator arms constitute standard treatments for patients with moderate to severe asthma, the exception being the formoterol/budesonide maintenance plus formoterol as needed arm in the trial by Rabe et al.[12]

These results demonstrate that the increased efficacy repeatedly shown for budesonide/formoterol maintenance and reliever therapy is not associated with any decrease in the safety of the treated patients, but rather the opposite. This new treatment regimen, with occasional use of high doses of ICS, was not associated with any increase in possible ICS-mediated adverse events in the budesonide/formoterol maintenance and reliever therapy group. Also, the rate of common $\beta_2$-agonist side effects was not increased following the use of formoterol as needed.

The ongoing debate on the safety of LABAs with respect to asthma mortality and morbidity originates largely from post-marketing surveillance trials with salmeterol, most recently the Salmeterol Multicentre Asthma Research Trial (SMART),[24] and subsequent meta-analyses[20] heavily influenced by that study. SMART showed an increased risk of asthma mortality in the LABA group (2.0 versus 0.5 asthma deaths per TTY in the LABA and placebo groups, respectively). However, only 47% of the patients were reported to have been prescribed ICS at baseline. Large pooled analyses by Sears et al. of over 68 000 asthmatic patients involved in AstraZeneca clinical trials with formoterol-containing products[25] (92% ICS users) and by Jaeschke et al. of 29 000 patients enrolled in trials with salmeterol plus ICS or formoterol plus ICS versus ICS alone[19] (100% ICS users) showed low rates of asthma mortality but, because of the low number of asthma-related deaths, no definite conclusions could be drawn.

The observations in the current analysis, relating to a new treatment strategy specific to the budesonide/formoterol combination, do not add data directly applicable to this LABA safety debate since the main analysis does not involve a direct LABA versus non-LABA comparison. However, we can state that the observed rate of asthma-related death in the budesonide/formoterol maintenance

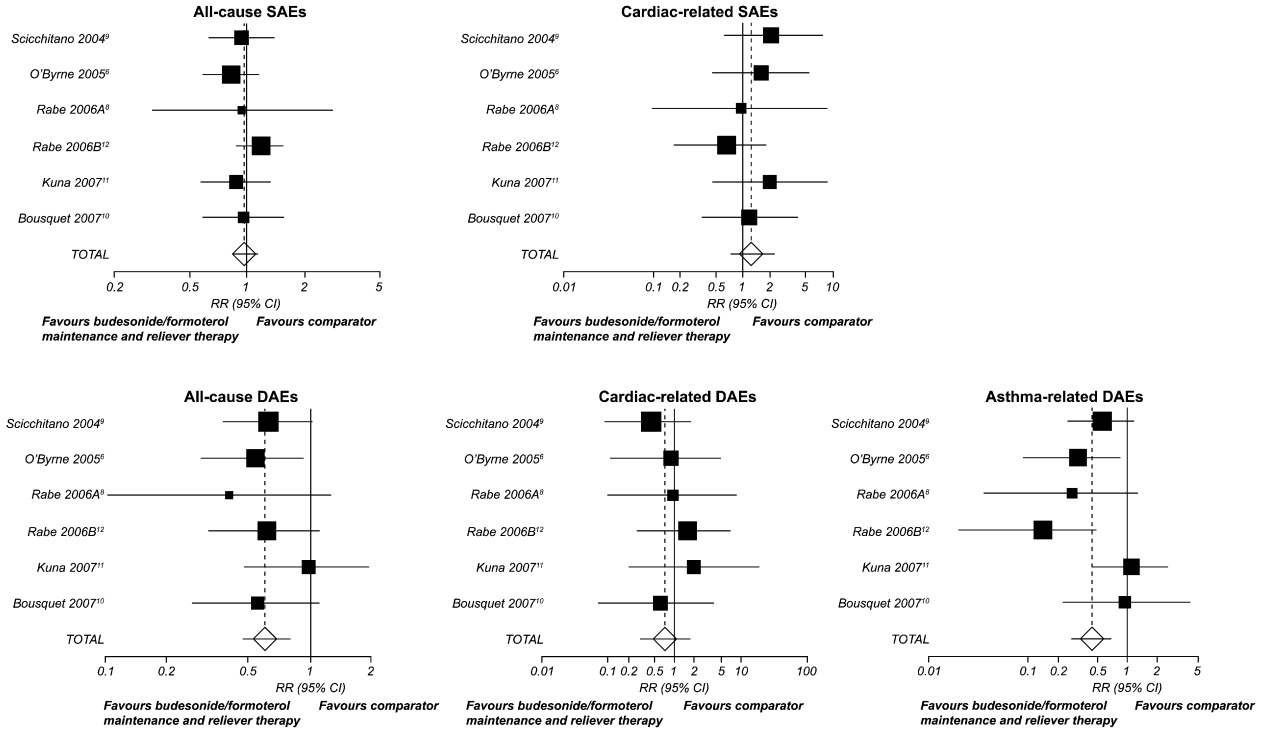


**Figure 4** Forest-plots of Mantel–Haenszel relative risks for secondary outcome events. CI = confidence interval; DAE = discontinuation due to adverse event; RR = risk ratio; SAE = serious adverse event.

**Table 4** Incidence of $\beta_2$-agonist- or inhaled corticosteroid-related adverse events of interest (serious and non-serious).

| Preferred term | Number (%) of patients reporting at least one adverse event | |
|---|---|---|
| | BUD/FORM maintenance and reliever therapy $N = 5584$ | Comparators $N = 8762$ |
| Dysphonia | 61 (1.1) | 91 (1.0) |
| Oral candidiasis | 58 (1.0) | 69 (0.8) |
| Tremor | 33 (0.6) | 67 (0.8) |
| Palpitations | 34 (0.6) | 37 (0.4) |
| Pneumonia[a] | 33 (0.6) | 68 (0.8) |
| Cataract | 3 (0.05) | 4 (0.05) |
| Glaucoma | 4 (0.07) | 3 (0.03) |

BUD/FORM = budesonide/formoterol.

[a] Pneumonia has been included for completeness due to the current debate on the relationship between pneumonia and inhaled corticosteroids in chronic obstructive pulmonary disease.

and reliever therapy group (100% ICS users) of one death in 3930 treatment years (rate 0.25 deaths per TTY) was low. In addition, it can be noted that in seven open-label trials (Vogelmeier et al.[23] plus six pooled trials with conventional best practice as comparator[16]) no asthma-related deaths were reported in over 4900 patients exposed to budesonide/formoterol maintenance and reliever therapy during over 2900 years of exposure. Furthermore, among these open-label trials, which bear a closer resemblance than double-blind trials to the real-world setting, asthma-related SAEs were numerically lower among patients treated with budesonide/formoterol maintenance and reliever therapy than among those on standard asthma treatments. Nevertheless, despite these reassuring findings, it is recognised that patients with significant co-morbidities are generally excluded from all of these trials, and ongoing pharmacovigilance with post-marketing surveillance is appropriate.

Our findings are consistent with other recent safety analyses of ICS/LABA combinations, which have concluded that adding a LABA to ICS is both effective and safe for the treatment of asthma,[26–29] and that the risk of asthma-related SAEs (mainly hospitalisations due to asthma) was lowered in the ICS/LABA groups compared with treatment with ICS alone.[25] The use of LABA in combination with an appropriate dose of ICS is consistent with recommendations in international guidelines and the labels approved by most regulatory authorities.

Treatment with budesonide/formoterol maintenance and reliever therapy has consistently shown similar or better current control and reduced future risk of exacerbations compared with guideline-recommended fixed-dose comparators. This has been achieved at a lower overall exposure to oral and systemic corticosteroids.[6,8–12] This analysis has addressed another component of future risk, namely medication adverse events.

Budesonide/formoterol maintenance and reliever therapy has been shown to be well tolerated and not associated with increased safety concerns, with lower or similar incidence of death and asthma-related SAEs compared with the fixed-dose comparators. These results also demonstrate that occasional use of high doses of formoterol, taken as needed at times of deteriorating asthma symptoms, delivered together with budesonide, does not increase the rate of asthma-related events but instead significantly lowers the risk. This is of particular importance, since one of the hypotheses for the potential risk of LABAs in asthma is that treatment with LABAs would cause $\beta_2$-receptor desensitisation and subsequent lack of response to bronchodilator therapy in emergency situations.[30] In this large clinical database there is no support for this hypothesis.

We conclude that the budesonide/formoterol maintenance and reliever therapy regimen[3] in randomised clinical trials is not associated with increased risk of cardiac- or asthma-related deaths or SAEs and is well tolerated, with anticipated class-related adverse events due to $\beta_2$-agonists or ICS. Compared with present fixed-dose alternatives, this strategy offers at least as good reduction of future risk of medication adverse events.

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## Supplementary data

Supplementary data associated with this article can be found in the on-line version, at doi:10.1016/j.rmed.2009.08.007.

## Conflict of interest

In the last five years, Dr. Sears has acted as speaker or consultant to several pharmaceutical companies including AstraZeneca, Centocor, GlaxoSmithKline, Merck, Nycomed and Schering-Plough, has received research grants from AstraZeneca and Merck, and holds an endowed chair in Respiratory Epidemiology jointly endowed by AstraZeneca and McMaster University. Dr. Radner is an employee of AstraZeneca.

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